Complete Summary

GUIDELINE TITLE

Guidance on the use of vinorelbine for the treatment of advanced breast cancer.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of vinorelbine for the treatment of advanced breast cancer. London (UK): National Institute for Clinical Excellence (NICE); 2002 Dec. 14 p. (Technology appraisal guidance; no. 54).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Advanced Practice Nurses
Nurses
Patients
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To examine the clinical effectiveness and cost-effectiveness of vinorelbine therapy for advanced breast cancer

TARGET POPULATION

Adults with relapsed advanced breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Vinorelbine

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
  - Tumour response
  - Progression free and overall survival
  - Symptom relief
  - Quality of life
  - Adverse effects of treatment
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews and Dissemination, University of York (See the "Availability of Companion Documents" field.)

Search Strategy

The following databases were searched for relevant literature:

- MEDLINE
- EMBASE
- Cancerlit
- BIOSIS
- Index to Scientific and Technical Proceedings (ISTP)
- Cochrane Controlled Trials Register (CCTR)
- Database of Abstracts of Reviews of Effectiveness (DARE)
- National Health Service Economic Evaluation Database (NHSEED)
- National Research Register (NRR)

More detailed information about the search strategy is presented in Appendix 1 of the Assessment Report (see the "Availability of Companion Documents" field).

Bibliographies of all included articles were searched for additional references. Manufacturer and sponsor submissions made to the National Institute for Clinical Excellence (NICE) were also reviewed to identify additional studies. The internet was searched for information on ongoing trials.

When updating the review (for the inclusion of non-comparative phase II studies) the original searches were rerun without the randomised controlled trial and economic evaluation methodological search filters. Methodological filters were not used in the original searches for the Biosis, Index to Scientific and Technical Proceedings (ISTP), Cochrane Controlled Trials Register (CCTR) and the National Research Register (NRR) databases, so the searches remained exactly the same for these databases.

Inclusion and Exclusion Criteria

Titles (and where possible abstracts) of studies identified from all searches and sources (see Appendix 1 of the Assessment Report [see the "Availability of Companion Documents" field]) were assessed independently by two reviewers for relevance. If either reviewer considered the paper to be potentially relevant, a full paper copy of the manuscript was obtained. Each full paper copy was reassessed for inclusion using the criteria listed below.

Studies that did not meet all of the criteria were excluded and their bibliographic details are listed in Appendix 2 of the Assessment Report (see the "Availability of Companion Documents" field), along with the reason for exclusion. Information relating to inclusion of trials highlighted by the industry submissions is presented in Appendix 11 of the Assessment Report (see the "Availability of Companion Documents" field). Any disagreements were discussed in order to obtain a consensus and if no agreement was reached a third reviewer was consulted.

Interventions

The following interventions were included:

Vinorelbine (Navelbine®, Pierre Fabre Ltd., Winchester, UK) alone or in combination with other agents versus systemic therapy without vinorelbine. When updating the review, vinorelbine was only considered when used as first line treatment for advanced breast cancer (ABC).

Participants

For the initial review, patients with breast cancer, encompassing all stages of disease, were included. Where possible the stage of disease was defined using the Simplified Union Internationale Contre le Cancer (UICC) staging system (see Appendix 3 of the Assessment Report [see the "Availability of Companion Documents" field]).

When updating the review only patients with advanced breast cancer (locally advanced [stage III] or metastatic [stage IV] disease) were included.

Study Design

The ultimate standard for the evaluation of medical treatments is the randomised controlled phase III clinical trial. For the evaluation of clinical effectiveness, only randomised controlled trials (RCTs) were initially included in the review.

For the update section of the review that was to include uncontrolled phase II studies of vinorelbine used as first line therapy for ABC, non-randomised studies such as cohort studies, case-control studies and case-series were included. However, the findings of these studies should be interpreted with caution because, in contrast to high-quality RCTs, confounding and selection bias often distorts the findings of such studies. Within the pharmaceutical industry, phase II studies represent the initial clinical investigation, which are usually single-arm studies involving roughly n=14 to 90 patients. Studies that include less than 14 participants, were therefore, excluded.

Cost-Effectiveness

To evaluate the cost-effectiveness of trastuzumab and vinorelbine the following economic evaluations were considered:

- Cost effectiveness analysis (CEA) (including cost-minimisation analysis [CMA] and cost consequence analysis [CCA])
- Cost-utility analysis (CUA)
- Cost-benefit analysis (CBA)

NUMBER OF SOURCE DOCUMENTS

Two randomised controlled trials (RCTs) investigated the use of vinorelbine monotherapy. Five RCTs investigated the use of vinorelbine in combination with other chemotherapy drug(s). Fourteen uncontrolled studies of vinorelbine monotherapy and fifty-one studies of combination therapy were included in the review. Four economic evaluations were included in the review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews and Dissemination, University of York (See the "Availability of Companion Documents" field.)

Data Extraction Strategy

Data extraction was conducted by one reviewer using predefined data extraction forms and checked by a second reviewer. Any disagreement was resolved by consensus, and if this was not reached, a third reviewer was consulted. Due to time constraints, only studies reported in English (for both effectiveness and economic data), German, Dutch, and French (for effectiveness data only) were included in the report. However, the search strategy included all languages and the bibliographic details of non-English language studies are presented in the tables of excluded studies (see Appendix 2 of the Assessment Report [see the "Availability of Companion Documents" field]).

The following types of data were extracted and summarised: specific details about the interventions, the population investigated, and the outcome measures used. Studies that have been reported in multiple publications were collated and reported only once.

Where sufficient data were presented, an estimation of the treatment effect, along with the 95% confidence interval (CI), was calculated for each individual study. Where possible this was done on an intention-to-treat basis. For dichotomous outcome measures, the relative risk (RR) was calculated. For time to event outcomes (e.g., survival), hazard ratios (HR) were not reported by included studies. The median values and any measures of variance are therefore presented.

In order to assess the economic data in terms of the clinical effectiveness of the intervention (i.e., the direction of the cost-effectiveness data and the magnitude of effectiveness data), each study was given a summary grading (A-I) according

to the level and direction of dominance (i.e., whether the intervention of interest should be preferred over the comparator). Extended dominance indicates that both the effectiveness data and the economic data support the use of either the intervention or the comparator and the decision on resource allocation is clear. When only the economic or the effectiveness data supports the intervention/comparator, the dominance is said to be partial or weak and a decision can still be made. However, if there is no dominance indicated then further incremental cost analysis may be required in order to estimate the incremental cost-effectiveness ratio. This is important in helping the decision making process. The matrix (Figure 1 of the Assessment Report [see the "Availability of Companion Documents" field]) illustrates all of the possible permutations, and was used to assign each study a summary grading.

Quality Assessment Strategy

The methodological quality of each included study was assessed using predefined checklists (see Appendix 4 of the Assessment Report [see the "Availability of Companion Documents" field]). Two reviewers conducted this process independently. Any disagreements were resolved by consensus and a third reviewer was consulted if required.

Methods of Analysis/Synthesis

Results of data extraction and quality assessment are presented in structured tables and also as a narrative summary. Studies are grouped according to the type of intervention (monotherapy or combination therapy) and study design used. The results from the uncontrolled studies (identified whilst updating the review) are compared to the overall findings of the randomised controlled trials (RCTs) that were included in the initial review.

Both RCTs and uncontrolled (phase II) studies were assessed for clinical diversity and, where appropriate, statistical heterogeneity. Where there was no significant diversity or statistical heterogeneity, pooled estimates of effects were calculated.

For the initial review, it was not possible to investigate the extent of publication bias due to the limited number of included studies. Sensitivity analyses were also not undertaken for the same reason. For the update review, publication bias among observational studies is evaluated using funnel plots.

A narrative summary of the cost effectiveness data is presented, considering the methods of analysis used, the sources of effectiveness and cost data, the quality of the economic evaluation, and the generalisability of the findings to the United Kingdom setting.

The number of excluded studies, along with the reason for exclusion is presented in the results section of the report. The bibliographic details of studies that did not meet the inclusion criteria (including those that included less than 14 participants and phase II studies of vinorelbine used as second line therapy for advanced breast cancer) have been tabulated, along with the reason for exclusion, and presented in Appendix 2 of the Assessment Report [see the "Availability of Companion Documents" field]).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Monotherapy

No studies of first-line vinorelbine monotherapy were available. Four economic evaluations of second-line vinorelbine monotherapy were reviewed. All four used a cost-utility framework and included the healthcare costs associated with treatment; one also included patient costs. Three studies compared the cost effectiveness of vinorelbine with taxane (paclitaxel or docetaxel) monotherapy. Only one of these studies was performed from a United Kingdom (UK) perspective. The fourth study, which was carried out in the United States and was reported only as an abstract, compared the use of vinorelbine monotherapy with capecitabine, 5-fluorouracil, and gemcitabine in patients resistant to anthracyclines and paclitaxel.

All four evaluations were performed using modeling techniques and estimated clinical effectiveness using either individual arms from more than one randomised controlled trials (RCT) or case series, as there were no trials comparing vinorelbine with taxanes.

Of the three fully reported studies, which compared vinorelbine with taxane monotherapy, one (the UK based evaluation) showed vinorelbine to be less effective and less expensive, one showed vinorelbine to be less effective and more expensive, and the third showed vinorelbine to be more effective and less expensive. The UK-based evaluation, which was sponsored by the manufacturer of docetaxel, found the incremental cost-effectiveness ratio for docetaxel over vinorelbine to be 14,500 pounds sterling per Quality-Adjusted Life-Year. The US-based study, found capecitabine to be the most cost-effective option.

Combination Therapy

No economic evaluations of first- or second-line combination vinorelbine therapy were available.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Vinorelbine monotherapy is not recommended as a first-line treatment for advanced breast cancer.
- Vinorelbine monotherapy is recommended as one option for second-line or later therapy for the treatment of advanced breast cancer when anthracycline-based regimens have failed or are unsuitable. The choice of appropriate second-line or later treatment for advanced breast cancer should be made jointly by the patient and the clinician responsible for treatment after an informed discussion of the relative benefits of the available drugs and their side-effect profiles.
- The present state of evidence does not allow the Institute to recommend the routine use of vinorelbine combination therapies.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of vinorelbine for advanced breast cancer

POTENTIAL HARMS

- The dose limiting toxicity of vinorelbine is mainly neutropenia. This commonly occurs between days 8-12, but is short lived and not cumulative.

- Other adverse effects include neurological problems (peripheral or autonomic neuropathy), gastrointestinal problems (constipation, diarrhoea, nausea/vomiting), allergic reactions and venous tolerance (local phlebitis and burning at injection site). Patients with neurological toxicity commonly experience peripheral parasthesia, loss of deep tendon reflexes, abdominal pain, and constipation. If neurosymptoms are severe, doses should be reduced. Motor weakness can also occur, which calls for discontinuation of treatment. Generally recovery of the nervous system is slow but complete. Other undesirable effects include alopecia (generally reversible). In addition, vinca alkaloids can cause severe irritation and care must be taken to avoid extravasation.

CONTRAINDICATIONS

CONTRAINDICATIONS

Vinorelbine is contraindicated in:

- Pregnancy
- Lactation
- Severe hepatic insufficiency not related to the disease process

Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation

- Clinicians with responsibility for treating people with advanced breast cancer should review their current practice in line with the guidance (see the "Major Recommendations" field).
- Local clinical guidelines, protocols, or care pathways on the care of people with breast cancer should incorporate the guidance.
- Local clinical audits on the management of breast cancer also could include measurement of compliance with accepted clinical guidelines or protocols.

IMPLEMENTATION TOOLS

Foreign Language Translations
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of vinorelbine for the treatment of advanced breast cancer. London (UK): National Institute for Clinical Excellence (NICE); 2002 Dec. 14 p. (Technology appraisal guidance; no. 54).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Dec

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Professor R. L. Akehurst, Dean, School of Health Related Research, Sheffield University; Professor David Barnett (Chairman) Professor of Clinical Pharmacology, University of Leicester; Professor Sir Colin Berry, Professor of Morbid Anatomy, St Bartholomew's and Royal London, School of Medicine; Dr Sheila Bird, MRC Biostatistics Unit, Cambridge; Professor Martin Buxton, Director of Health Economics Research Group, Brunel University; Dr Karl Claxton, Lecturer in Economics, University of York; Professor Sarah Cowley, Professor of Community Practice Development, Kings College, London; Mr Chris Evennett, Chief Executive, Mid-Hampshire Primary Care Group; Professor Terry Feest, Clinical Director and Consultant, Nephrologist, Richard Bright Renal Unit, and Chairman of the UK Renal Registry; Professor Gary A Ford, Professor of Pharmacology of Old Age and Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle; Mrs Sue Gallagher, Chief Executive, Merton, Sutton and Wandsworth, Health Authority; Dr Trevor Gibbs, Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline; Mr John Goulston, Director of Finance, The Royal Free Hampstead NHS Trust; Professor Philip Home, Professor of Diabetes Medicine, University of Newcastle; Dr Terry John, General Practitioner, The Firs, London; Dr Diane Ketley, Research into Practice Programme Leader, NHS Modernisation Agency; Dr Mayur Lakhani, General Practitioner, Highgate Surgery, Leicester and Lecturer, University of Leicester; Mr M Mughal, Consultant Surgeon, Chorley and South Ribble NHS Trust; Mr James Partridge, Chief Executive, Changing Faces; Professor Philip Routledge, Professor of Clinical Pharmacology, University of Wales College of Medicine; Professor Andrew Stevens (Vice Chairman) Professor of Public Health, University of Birmingham; Dr Cathryn Thomas, General Practitioner, Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Guidance on the use of vinorelbine for the treatment of advanced breast cancer. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2002 Dec. 2 p. (Technology appraisal 54). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- A rapid and systematic review of the clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer. Assessment report. NHS R&D HTA Programme; 2002 Feb. 293 p. Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0141. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Guidance on the use of vinorelbine for the treatment of advanced breast cancer. Information for patients. London (UK): National Institute for Health and Clinical Excellence (NICE); 2002 Sep. 6 p. (Technology appraisal 54).

Electronic copies: Available in English and Welsh in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N0143. 11 Strand, London, WC2N 5HR.

NGC STATUS

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